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S E M I N A I R E

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« Insulin conformations and storage: Molecular simulation of the role of divalent cations and neurotransmitters »

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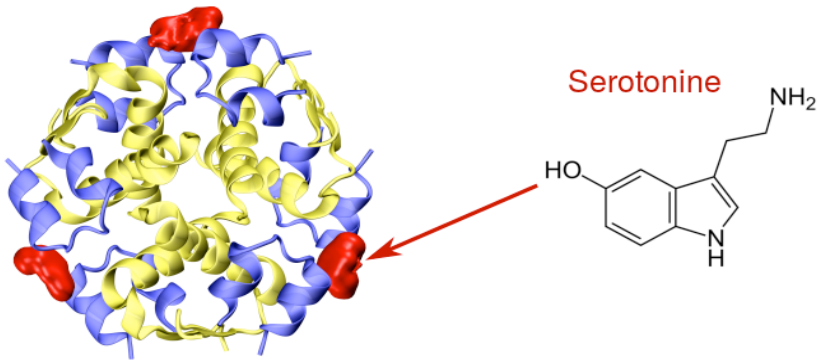
Insulin is stored in the pancreas in a hexameric form, which presumably protects it from chemical or physical damage. This is realized in the presence of high concentrations not only of divalent cations (Ca2+, Mg2+ and Zn2+) but also of phenolic neurotransmitters, such as dopamine or serotonine. Previous studies have shown that Zn2+ ions play a key role in promoting insulin hexamerization, and that phenol induces a change of the insulin hexamer conformation. However, the impact of other divalent cations and of neurotransmmiters remains elusive. Here, we explore the effect of the complex environment in the pancreatic vesicles on the insulin storage conformation, with the ultimate aim of both better understanding the in vivo storage conditions of insulin, as well as optimizing them for durable pharmaceutical formulations.

To this end, we combine state-of-the art simulation techniques with X-ray crystallography and electrophoresis experiments. This allows us to explore ion binding to different insulin multimers and to examine how the insulin T-R conformational transition is affected by its multimeric state and the presence of neurotransmitters and ions. [1] Specific attention is paid to the description of ion-biomolecules interactions which are poorly captured by standard force field. We thus develop a new interaction model, benchmarked on reference ab initio molecular dynamics simulations and neutron-scattering experiments performed on model systems. [2] This approach implicitly takes into account the electronic polarization in a mean field way, which considerably improves the description of cations-biomolecule interactions in simulations. [3]



[1] V. Palivec et al. , J.Biol.Chem., **292**, 8342 (2017)
[2] T. Martinek et al., J. Chem. Phys., **148**, 222813 (2018)
[3] E. Duboue-Dijon, et al., J. Phys. Chem. B, 122, 5640-5648 (2018)

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